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SYSTEMATIC REVIEW

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Clinical efficacy and safety of interleukin-1 blockade in the treatment of patients with COVID-19: a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Objective: This study evaluated the clinical efficacy and safety of interleukin-1 (IL-1) blockade for patients with COVID-19.

Methods: The PubMed, Web of Science, Ovid Medline, Embase and Cochrane Library databases were searched for relevant articles from their inception to 25 September 2022. Only randomized clinical trials (RCTs) that assessed the clinical efficacy and safety of IL-1 blockade in the treatment of patients with COVID-19 were included.

Results: This meta-analysis included seven RCTs. No significant difference in the all-cause mortality rate of patients with COVID-19 was observed between the IL-1 blockade and control groups (7.7 vs. 10.5%, odds ratio [OR] = 0.83, 95% confidence interval [CI] 0.57–1.22; I^2 = 18%). However, the study group was at significantly lower risk of requiring mechanical ventilation (MV) compared with the control group (OR = 0.53, 95% CI 0.32–0.86; I^2 = 24%). Finally, the risk of adverse events was similar between the two groups.

Conclusions: IL-1 blockade does not provide increased survival benefits in hospitalized patients with COVID-19, but it may reduce the need for MV. Furthermore, it is a safe agent for use in the treatment of COVID-19.

KEY MESSAGES

- This systematic review and meta-analysis of randomized clinical trials (RCTs) evaluated the clinical efficacy and safety of interleukin-1 (IL-1) blockade for patients with COVID-19.
- Based on the analysis of six RCTs, no significant difference in the all-cause mortality rate of patients with COVID-19 was observed between the IL-1 blockade and control groups.
- The study group using IL1 was associated with a significantly lower risk of requiring mechanical ventilation compared with the control group.
- The risk of adverse events was similar between the study and the control groups.

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Anakinra; canakinumab; COVID-19; interleukin-1; SARS-CoV-2

1. Introduction

Since the first outbreak of SARS-CoV-2 in Wuhan, China, at the end of 2019, COVID-19 has rapidly become a global health concern [1]. During the following 2-year period, more than 400 million cases, including more than 6 million resulting in death, have been reported by the World Health Organization [2]. The mortality of patients with COVID-19 is approximately 2%, most cases of severe or critical COVID-19 can be attributed to a cytokine storm following the exaggerated inflammatory response caused by SARS-CoV-2 infection [2–4]. Furthermore, such hyperactivated immune response can lead to acute lung injury, systemic inflammatory response syndrome, acute respiratory distress syndrome (ARDS) or multiple organ dysfunction syndromes, as

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well as mortality [5,6]. The mechanism of COVID-19 causing ARDS is complicated, which can involve angiotensin-converting enzyme 2 protein, triggering of Fas/FasL signalling pathway to promote apoptosis, JAK/STAT pathway, NF-κB pathway, type I interferon, activation of the immune response, and cytokine storm [7]. Monocytes and macrophages would play a substantial part in the body's defence against SARS-CoV-2 infection, including releases of interleukin-1 (IL-1) and IL-6, which would have particularly crucial roles within the hyperactivated immune response to SARS-CoV-2 infection [8–15]. Similar to IL-6 blockade with tocilizumab, which has exhibited clinical efficacy in the treatment of hospitalized patients with COVID-19 [16], IL-1 blocking agents may help suppress the COVID-19-associated dysfunctional immune response and are also proposed to be a potential therapy for patients with hyperinflammatory COVID-19 [13].

IL-1 is the prototypic pro-inflammatory cytokine, and IL-1α and IL-1β were the two major forms within this family, and the IL-1 cytokine family has a pivotal role in the induction of cytokine storm due to uncontrolled immune responses in COVID-19 infection [8,17]. Several monoclonal antibodies or inhibitors targeting the IL-1 receptor have been developed to inhibit proinflammatory molecules and influence the activation of the body's innate immune response [18]. Anakinra is a recombinant IL-1 receptor antagonist and can help prevent their proinflammatory activity [19]; several observational studies have demonstrated that it can provide survival benefits and reduce the need for mechanical ventilation (MV) in patients with severe COVID-19 [19–21]. Canakinumab, a fully human monoclonal antibody targeting IL-1β, is another promising therapeutic option for attenuating the dysregulated immune response to severe COVID-19 [18]. An observational study has demonstrated that compared with the standard of care (SOC), canakinumab could rapidly restore normal oxygen status, decrease the need for MV, and lead to earlier hospital discharge and favourable outcomes [22]. In addition to observational studies, the results of several randomized clinical trials (RCTs) investigating the usefulness of IL-1 blockade for treating COVID-19 have been reported recently [23–27]. However, their findings are not consistent. Therefore, we conducted this systemic review and meta-analysis of RCTs to evaluate the clinical efficacy and safety of IL-1 blockade for patients with COVID-19.

2. Methods

2.1. Study search and selection

The PubMed, Web of Science, Ovid Medline, Embase and Cochrane Library databases were searched for relevant articles from their inception to 25 September 2022. We used the following search terms: 'COVID-19', 'coronavirus infections', 'coronavirus', 'corona infection', 'SARS-CoV-2', 'interleukin 1 receptor antagonist', 'IL-1Ra', 'kineret', 'arcalyst', 'canakinumab', 'ilaris', 'anakinra' and 'rilonacept'. Only RCTs that assessed the clinical efficacy and safety of IL-1 blockade for the treatment of patients with COVID-19 were included. We also manually searched for additional eligible articles from the reference lists of relevant articles. This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines [28]. Two authors (SHL and CCL) independently screened and identified articles to avoid bias. A third author (SHH) was consulted in cases of disagreement over the same publication and made the final decision. The protocol of the systematic review and meta-analysis was registered on PROSPERO (CRD42022300811).

2.2. Eligibility criteria

Studies were included if they met the following criteria: (i) included patients with COVID-19, (ii) used anti-IL-1 cytokine family as an intervention, (iii) used a placebo or the SOC as a comparator, (iv) involved an RCT and (v) reported clinical efficacy as a study outcome. The following were excluded: (i) conference posters, case reports, case series and observational studies; (ii) single-arm studies; (iii) studies that did not report the outcomes of interests; (iv) studies that did not compare outcomes for IL-1 blockade with a placebo or control; (v) pharmacokinetic studies; and (vi) *in vitro* studies.

2.3. Data extraction

The following data were extracted from each included study separately by two authors (CCL and SPC): year of publication, study design, the IL-1 blockade regimen, clinical outcomes and risk of adverse events (AEs). If the extracted data were inconsistent, a third author (LCL) was consulted. The primary outcome was all-cause mortality at day 28. Secondary outcomes were the rate of clinical recovery at day 14 and survival to discharge, the need for noninvasive ventilation (NIV) or high-flow nasal cannula (HFNC) and MV at day 28, and the risk of AEs.

2.4. Data analysis

We used the Cochrane risk-of-bias tool 2.0 [29] to assess the quality of the included studies and risk of

bias and Review Manager (version 5.3; Nordic Cochrane Center, Copenhagen, Denmark) for statistical analysis. The degree of heterogeneity was evaluated using Q statistics generated by a χ^2 test, and the I^2 measure was used to assess statistical heterogeneity. Heterogeneity was defined as significant when $p < .10$ or $I^2 > 50\%$. A fixed-effects model was applied for homogeneous data, and a random-effects model was applied for heterogeneous data. We calculated pooled odds ratios (ORs) and 95% confidence intervals (CIs) for analysing outcomes of interests.

3. Results

3.1. Characteristics of the studies

The search strategy initially yielded 416 references. After excluding 140 duplicate articles, 276 articles were screened; finally, 11 articles were identified for a full-text review to assess eligibility after excluding the remaining 265 articles based on the title and abstract. Only seven RCTs [23–27,30,31] were designed to compare the clinical efficacy and safety of IL-1 blockade and placebo plus SOC in the treatment of patients with SARS-CoV-2 and were thus included in this meta-analysis (Figure 1 and Supplementary Appendix 1). Overall, this meta-analysis involved a total of 1650 patients, including 884 in the IL-1 blockade group and 732 in the control group. Among the patients receiving IL-1 blockade, 628 had received anakinra and 256 canakinumab. The characteristics of the included studies and patients are summarized in Table 1. Except for one single-centre study [25], the remaining six were multicentre studies [23,24,26,27,30,31]. In addition, two were multinational studies [26,27], and the remaining five were conducted in a single country: France [23,31], Belgium [24], Iran [25] and the United States [30]. Only one study involved patients with mild COVID-19 [23]; the other six had enrolled patients with moderate-to-severe COVID-19 [24–27,30,31]. The anakinra dosage and treatment duration varied in five studies [23–26,31], but canakinumab was used once only in two studies [27,30]. The risk of bias for each study is presented in Figure 2. Bias due to deviations from intended interventions was noted in three RCTs [23–25], in which the contents did not specify 'were cares and trial personnel aware of participants' during the studies. Another bias due to the randomization process was observed in two studies [25,30], in which the contents did not specify the allocation sequence.

Figure 1. Flow diagram of study selection.

Table 1. Characteristics of the included randomized clinical trials.

Study	Design	Sites	Patients	Anakinra or canakinumab regimens	Comparator	No. of patients	
						Study group	Control group
CORIMUNO-19 Collaborative group, 2021 [23]	Open-label, randomized controlled trial	16 hospitals in France	Mild-to-moderate COVID-19	200 mg of anakinra administered intravenously twice a day on days 1–3, then 100 mg twice on day 4, and 100 mg once on day 5	Usual care	59	55
Declercq et al. [24]	Open-label, randomized controlled trial	16 hospitals in Belgium	Hospitalized patients with COVID-19, hypoxia and signs of cytokine release syndrome	100 mg of anakinra administered subcutaneously once a day for 28 days or until hospital discharge	Standard of care	112	230
Kharazmi et al. [25]	Open-label, randomized controlled trial	1 hospital in Iran	Severe COVID-19 with elevated CRP	100 mg of anakinra administered intravenously once a day for 14 days or until hospital discharge	Standard of care	15	15
Kyriazopoulou et al. [26]	Double-blind, randomized controlled trial	29 hospitals in Greece and 8 in Italy	Moderate-to-severe COVID-19	100 mg of anakinra administered subcutaneously once a day for 7–10 days	Standard of care	405	189
NCT04365153 [30]	Double-blind, randomized controlled trial	45 hospitals in the US	Hospitalized patients with COVID-19 with elevated troponin and C-reactive protein levels	Single 300-mg or 600-mg dose of canakinumab administered intravenously	Placebo	29	16
Caricchio et al. [27]	Double-blind, randomized controlled trial	39 hospitals in Europe and the US	Hospitalized patients with COVID-19 pneumonia, hypoxia and systemic hyperinflammation	Single 450-mg dose of canakinumab administered intravenously for body weights of 40 to <60 kg, 600 mg for 60–80 kg, and 750 mg for >80 kg	Placebo	227	227
Audemard-Verger et al. [31]	Open-label, randomized controlled trial	20 hospitals in France	Hospitalized patients with COVID-19 pneumonia, hypoxia, systemic hyperinflammation and treated with antibiotics	Anakinra 400 mg/day (100 mg every 6 h) during 3 days and then 200 mg/day (100 mg every 12 h) during 7 days	Standard of care	37	34

3.2. Mortality

A pooled analysis of the seven included studies [23–27,30,31] revealed that the all-cause mortality rate of patients with COVID-19 in the IL-1 blockade group was lower than that of the control group (7.7% vs. 10.5%). However, the difference did not reach statistical significance (OR = 0.83, 95% CI 0.57–1.22; I^2 = 18%; Figure 3). A sensitivity analysis after eliminating one study and then repeated analysis of all the other studies using a random-effects model revealed the same findings. In the subgroup analysis of the four RCTs focusing on anakinra, no significant difference was observed between the study and control groups (OR = 0.88, 95% CI 0.56–1.38; I^2 = 45%) [23–26,31]. Similarly, the subgroup analysis of the two RCTs focusing on canakinumab identified no significant difference in mortality between the two groups (OR = 0.73, 95% CI 0.36–1.47; I^2 = 0%) [27,30].

3.3. Secondary outcomes

Five studies [23,25–27,31] reported the rate of patients requiring MV, and the pooled analysis revealed that the study group had a significantly lower risk of requiring MV than did the control group (OR = 0.53, 95% CI 0.32–0.86; I^2 = 24%; Figure 4). These five studies [23,25–27,31] reported patients requiring NIV or HFNC, and the pooled analysis revealed a similar risk between the IL-1 blockade and control groups (OR = 0.95, 95% CI 0.53–1.70; I^2 = 0%). Four studies [23,25,27,31] reported the rate of survival to discharge, and the pooled analysis indicated that the study group had a significantly higher rate of survival to discharge than the control group did (OR = 1.59, 95% CI 1.08–2.35; I^2 = 0%). Another three RCT reported the rate of clinical recovery, and the pooled analysis revealed a similar risk between the IL-1 blockade and control groups (OR = 1.40, 95% CI 0.64–3.47; I^2 = 83%).

Finally, no significant difference was observed between groups receiving IL-1 blockade and placebo plus SOC in terms of the risk of AEs (OR = 1.15, 95% CI 0.74–1.79; I^2 = 54%), serious AEs (OR = 0.89, 95% CI 0.62–1.27; I^2 = 0%), clots (OR = 0.83, 95% CI 0.37–1.86; I^2 = 0%), thromboembolism (OR = 0.78, 95% CI 0.36–1.68; I^2 = 0%), acute kidney injury (OR = 0.72, 95% CI 0.39–1.33; I^2 = 0%) or infection (OR = 1.01, 95% CI 0.47–2.17; I^2 = 68%; Figure 5).

4. Discussion

In this meta-analysis, seven RCTs [23–27,30,31] were reviewed to assess the efficacy and safety of IL-1 blockade in the treatment of hospitalized patients with COVID-19. Overall, adding IL-1 blockade to treatment

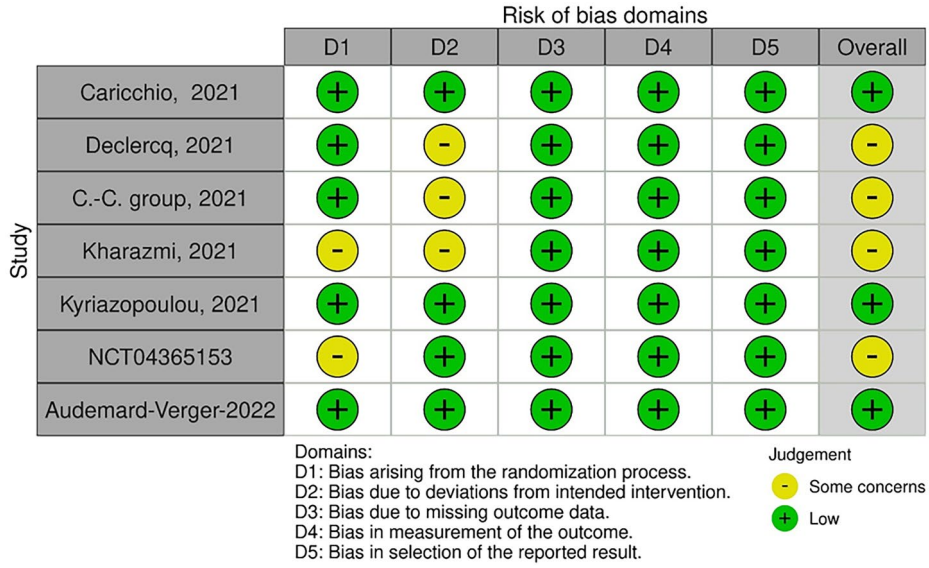

Figure 2. Summary of the bias risk in each domain.

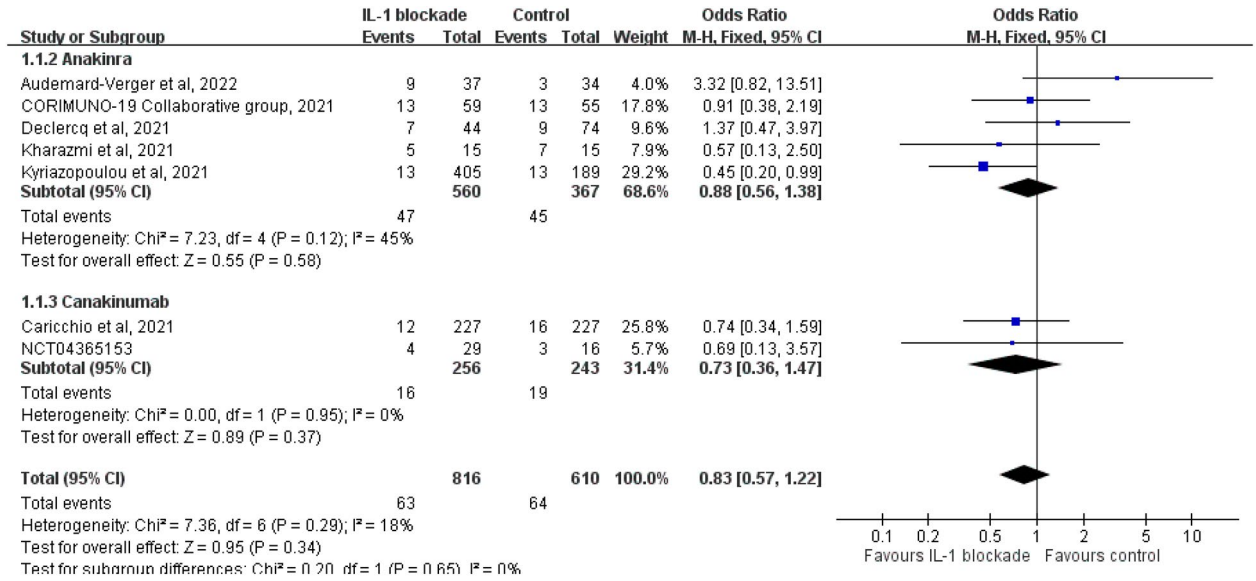

Figure 3. Forest plot of the all-cause mortality rate between IL-1 blockade and control group.

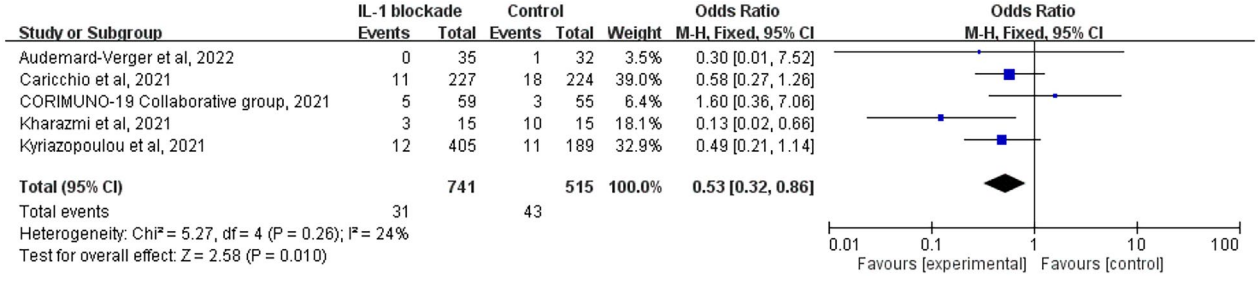

Figure 4. Forest plot of the risk of requiring mechanical ventilation between IL-1 blockade and control group.

regimens did not significantly reduce the mortality of patients with COVID-19; this finding is supported by the following evidence: first, the all-cause mortality rate of patients receiving IL-1 blockade was similar to that of the control groups. Second, this finding remained unchanged following leave-one-out analyses.

In a further subgroup analysis based on different types of IL-1 blockade (anakinra and canakinumab), the findings also remained unchanged. The analyses of mortality were based on homogeneous data, with $I^2 < 50\%$. Additionally, compared with placebo plus SOC, IL-1 blockade did not significantly reduce the rate of NIV and HFNC use and did not contribute to an increase in clinical recovery. By contrast, we revealed that administering IL-1 blockade could help decrease the necessity of MV and also enhance the rate of survival to discharge. However, these findings were based on the analysis of only five and four RCTs, respectively. In summary, our findings do not support the use of IL-1 blockade in the treatment of patients with COVID-19, but further RCTs are warranted to validate our findings.

These findings are not consistent with other meta-analyses [32–34]. A patient-level meta-analysis, including eight observational studies and one RCT, demonstrated that mortality was significantly lower in patients treated with anakinra (38/342 [11%]) than in those receiving SOC with or without placebo (137/553 [25%]; 11 vs. 25%, adjusted OR = 0.32, 95% CI 0.20–0.51) [32]. Another meta-analysis [33] involving two RCTs and four observational studies revealed that anakinra was associated with a relatively low risk of

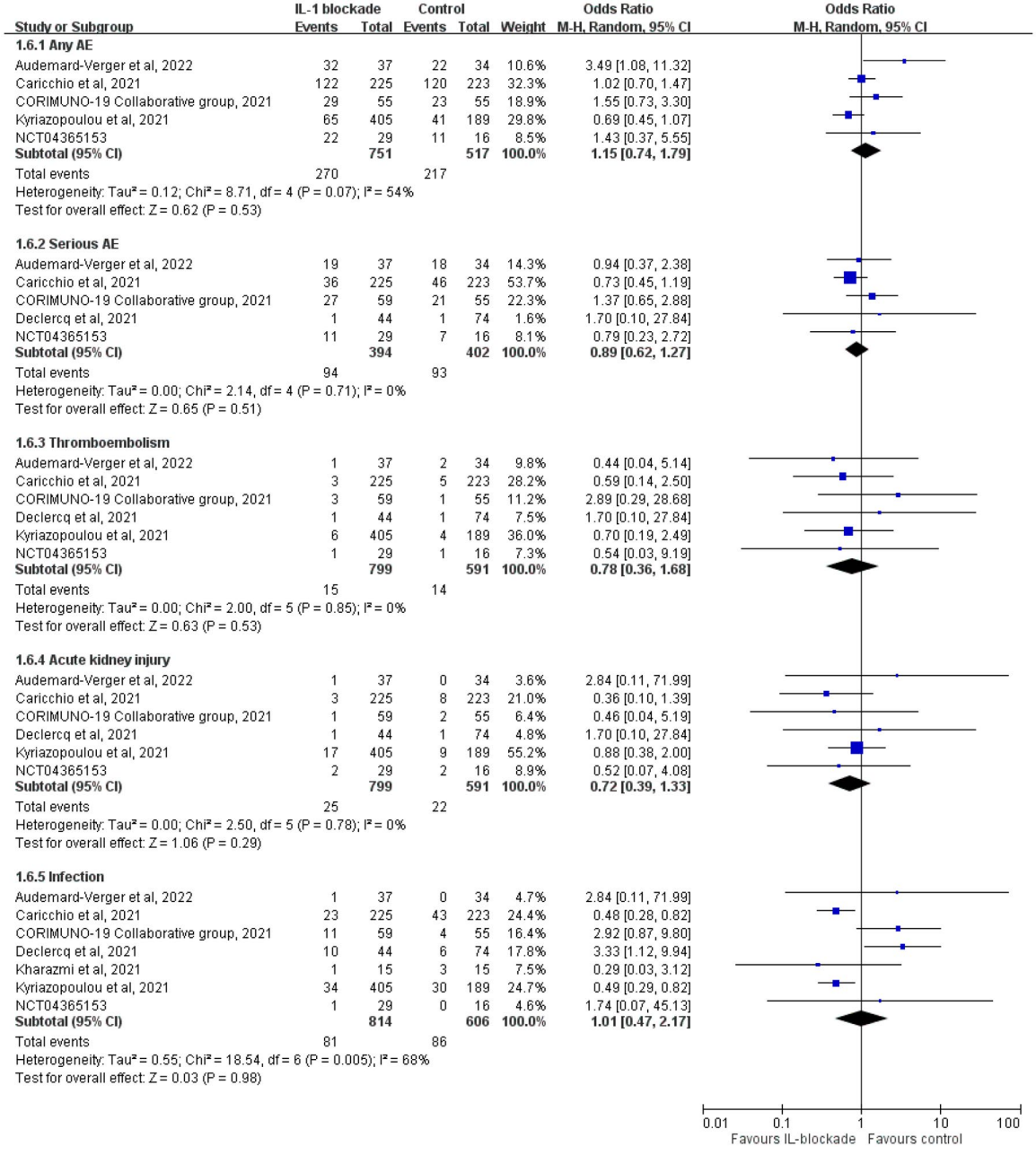

Figure 5. Forest plot of the risk of adverse event between IL-1 blockade and control group.

death (hazard ratio = 0.47, 95% CI 0.34–0.65). In contrast to previous meta-analyses [32–34], our findings were based on the meta-analysis of seven RCTs using more recent data. Therefore, the confounding factors would be minimized in the present study.

In addition, this meta-analysis assessed safety issues associated with IL-1 blockade. Compared with placebo plus SOC, IL-1 blockade was not associated with a higher risk of AEs (any AE, serious AEs and other specific AEs), including thromboembolism, acute kidney injury and infection. These findings are consistent with those of a study [32] indicating that anakinra was not associated with an increased risk of secondary infection (OR = 1.35, 95% CI 0.59–3.10; I^2 = 79%) or thromboembolic events and another study [34] revealing no difference in the risk of AEs, including liver dysfunction (OR = 0.75, 95% CI 0.48–1.16) and bacteraemia (OR = 1.07, 95% CI 0.42–2.7). One RCT also reported the risks of serious AEs were similar between anakinra and standard care [31], in which only each episode of pulmonary embolism, bacterial pneumonia, hepatic cytolysis and sudden death among 37 patients receiving anakinra. Another study reported that the most common AE were ARDS (n = 11), followed by bacterial sepsis (n = 10), hepatic cytolysis (n = 7), multiple organ failure (n = 3), pulmonary embolism (n = 3) and each one of acute renal failure, anaemia, coronary syndrome, cholestasis, neutropenia, fungal sepsis, gastrointestinal bleeding and myeloma, among 59 patients receiving anakinra [23]. Therefore, our findings indicate that IL-1 blockade is a safe and tolerable agent for the treatment of patients with COVID-19.

This study has several limitations. First, only seven RCTs were included, and the sample sizes were small. Second, although most of our analyses were based on data with low heterogeneity, several significant differences, such as the severity of infection in the enrolled patients and the IL-blockade regimens used, were identified in the included studies. Third, the phase of COVID-19 is crucial to obtain an adequate response to the drugs and IL-1 blockade was supposed to work only in the second phase of the disease, when the actor of the damage is the immune system. Therefore, we did a subgroup analysis of patients with elevated CRP or sign of cytokine storm or systemic hyperinflammation and the outcome analysis about mortality remained unchanged (OR = 1.02, 95% CI 0.62–1.67; I^2 = 11%). However, we still need further study to investigate the usefulness of IL-1 blockade in the stage of hyperinflammation. Fourth, we only included two RCTs focusing on canakinumab, and did not find its clinical benefit. In contrast, several cohort studies [35–37] reported that canakinumab therapy might help improve the oxygenation, reduction in the systemic inflammatory response and mortality. Further RCT is needed to clarify the role of canakinumab. Finally, many studies investigating the usefulness of IL-1 blockade are ongoing (Supplementary Appendix 2), so further meta-analyses are warranted after more studies report their findings.

In conclusion, although IL-1 blockade did not provide increased survival benefits in hospitalized patients with COVID-19, it may reduce the need for MV. Furthermore, it is a safe agent for use in the treatment of COVID-19.

Author contributions

Conception: SHL, CKH, SPC, LCL and CCL. Study design: SHL, CKH, SPC, LCL and CCL. Analysis and interpretation: SHL, CKH, SPC, LCL and CCL. Drafting or writing: SHL, CKH, SPC, LCL and CCL. Substantial revision or critical review: LCL and CCL. All authors have agreed on the journal to which the article will be submitted; have reviewed the article; and have agreed on all versions of the article before submission, during revision and during submission for publication and any significant changes introduced at the proofing stage. In addition, all authors agree to take responsibility for the content of the article and to resolve any questions raised about the accuracy or integrity of the published work.

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Data availability statement

All the data were obtained from the included studies.

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